“Assisted” Reshaping of the Fetal Heart?

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Dramatic developments in medical imaging technologies over the past 40 years mean that we can now collect unprecedented amounts of information on cardiac and vascular structure and function. Fetal cardiac imaging, because of its requirement to image hearts on a very small scale while coping with both unpredictable movement and a rapid pulse rate, has provided the extreme test of these emerging technologies. During this period, there has been a similarly unprecedented technical evolution in medical care of the earliest stages of life. Three major developments included the following: (1) the emergence of assisted reproduction technologies (ARTs) in the late 1970s; (2) dramatic reductions in maternal and offspring mortality after pregnancy complications; and (3) the routine survival of infants, born prematurely, from very early in pregnancy. This has resulted in a cohort of individuals, now entering adult life, whose embryonic, fetal, and neonatal cardiovascular development occurred within a unique perinatal environment. The implications for the long-term health of these offspring have only recently started to be considered. Fortuitously, the parallel technical advances in imaging over this time provide us with the tools to deliver insights into the issue.

Perinatal Environment and Cardiovascular Structure and Function

Interest in how perinatal environment may influence cardiac and vascular structure and function developed in the mid-1990s with evidence not only of links between birthweight and later cardiovascular disease risk but, more specifically, of differences in vascular responses in children related to size at birth. It has become clear that these changes were both evident from very early in life and extended into adulthood. Furthermore, the functional variation is closely associated with changes in vascular structure. The cause of the low birthweight that underlies these vascular variations has also been investigated, which led to the observation that a proportion of the association is attributable to low birthweight as a result of prematurity rather than growth restriction per se. Furthermore, other pregnancy complications that drive preterm birth and influence fetal growth, such as preeclampsia, have been identified to have specific vascular risks for the offspring.

Very recently, evidence has emerged of cardiac, as well as vascular, differences related to perinatal environment, and the differences are quite profound. Crispi et al used ultrasound imaging to provide the first evidence of changes in left ventricular size and shape in children who had been born with growth restriction. Importantly, earlier this year, we demonstrated that perinatal associations with the heart can extend beyond childhood into adult life, which increases the likelihood that they are of real clinical relevance. Using cardiovascular magnetic resonance, we identified specific alterations in left ventricular size, shape, and function in young adults related specifically to preterm birth. This study also provided insights into the long-term independent impact of other pregnancy-related factors, such as preeclampsia, on cardiac function, with differences similar to those observed in the mothers. Most recently, the first evidence has emerged that perinatal factors have an even greater influence on the right ventricle.

In this issue of Circulation, Valenzuela-Alcaraz et al add ARTs to the list of perinatal factors that may have an influence on cardiac structure and function. Differences in vascular structure have been linked previously with ARTs in childhood, but the cardiac changes are new. Furthermore, Valenzuela-Alcaraz et al have been able to extend the imaging window back into neonatal and even fetal life to provide evidence that cardiac changes are already apparent before birth.

Why Should ARTs Associate With Cardiac Shape?

The authors propose that epigenetic changes related to the technology at the time of conception could lead to permanent reprogramming of cardiac development. Although such a proposal is consistent with current experimental programs in the developmental origins of disease, there is, at present, no data to support such a hypothesis. The time course and stability for epigenetic changes are not established, and which particular pathways may lead to the specific cardiac changes is speculative. What appears more striking is the similarity in observed cardiac changes in those born after ARTs to those born with growth restriction and after prematurity.

The description of more dramatic changes in right ventricular size and function mimics the patterns we observed in relation to prematurity. The globular heart shape mirrors those the authors described previously in children with growth restriction and match the computational models built from our own datasets from adults born preterm. Indeed, the authors comment that the children born after the use of ARTs tend to be born early and with a degree of growth restriction, and it seems rational to suggest that a common biological
factor drives common cardiac changes in the different situations. Most of the perinatal factors linked with differences in cardiac geometry and function are associated with alterations in blood flow, either in utero or at the time of birth, and have also been linked with changes in pulmonary and systemic vascular structure and function.\(^{9,18,19}\) Both of these factors could lead to altered hemodynamics and result in common patterns of in utero cardiac remodeling. If so, the authors may have a stronger argument for an epigenetic unifying hypothesis related to programming of vascular function.\(^{20}\)

A key issue to understand is the relevance of the altered cardiac structure and function to long-term health. In adult life, the differences in mass and function observed in young adults, if seen in relation to other cardiovascular diseases such as hypertension or heart failure, would be associated with significant increases in risk of mortality.\(^{14}\) To what extent ART contributes to any shift in risk, as opposed to the associated complications of growth restriction, prematurity, or preeclampsia, also needs additional evaluation. The correct emphasis can then be placed on the most appropriate perinatal risk markers so that, ultimately, targeted advice can be developed to minimize cardiovascular disease risk for the offspring.

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